REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Amendments

In response to the Examiner's inquiry, claims 1-8 and 12-16 were pending in the application. In the preliminary amendment filed with the application, reference to claims "1-9 and 12-16" being pending after earlier canceling claim 9 was inadvertent. Claim 9 was canceled according to the instructions in the preliminary amendment.

Claims 1-8 and 12-16 were pending in this application. However, Applicants request that claims 1-8 and 12-16 be canceled without prejudice or disclaimer and request the entry of new claims 17-39.

New claim 17 replaces former claim 1, and has been amended to recite that the product claimed has a synergistic antineoplastic effect in mammals. Support for the amendment can be found at, *inter alia*, page 2, line 27 through page 3, line 4; page 3, lines 9-13. New claim 18 depends from claim 17, reciting a pharmaceutically acceptable carrier or excipient. Support for the amendment can be found at, *inter alia*, page 5, lines 26-28. New claim 19 recites the product of claim 17 or 18 wherein treatment of tumors occurs in a human. Support for the amendment can be found in, *inter alia*, the original claims. New claim 20 replaces former claim 2. No amendments have been made other than correction of the claim's dependence from new claims 17 or 18. The original claims provide support for dependence from new claim 17, directed to mammals, and new claim 18, directed to humans. New claims 21 and 22 replace former claims 3 and 4, respectively. No amendments have been made other than correction of the claims' dependence from new claims 17 or 18. The original claims provide support for dependence from new claim 17, directed to mammals, and new claim 18, directed to humans.. New claim 23 and 24 replace former claim 5 and 6, respectively. Only the dependency of these claim has been changed from former claims 3 and 4, respectively, to new claims 21 and 22, respectively.

New claim 25 replaces former claim 7 The claim has been mended to recite that the pharmaceutical composition has a synergistic antineoplastic effect in mammals when administered simultaneously, separately or sequentially. Support for the amendment can be found at, *inter alia*, page 2, line 27 through page 3, line 4; page 3, lines 9-13. New claim 26 recites the pharmaceutical composition of claim 25 wherein the synergistic antineoplastic effect occurs in a human. Support for the claim can be found at, *inter alia*, page 2, lines 19-32 . New claim 27 replaces former claim 8. The dependency of the claim has been changed. New claim 28 replaces former claim 12. The claim has been amended to recite that the method claimed exhibits its effects in mammals. Support for the amendment can be found in, *inter alia*, the original claims. New claim 29 recites that the method of new claim 28 exhibits it effects in humans. Support for the amendment can be found in, *inter alia*, the original claims. New claim 30 replaces former claim 13. Only the dependency of the claim has been changed.

New claim 31 recites that the method of claim 28 or 29 is carried out by the simultaneous, separate or sequential administration of the alkylating anthracycline of formula Ia or Ib and the antimetabolite compound I. Support for the claim can be found at, *inter alia*, page 3, lines 5-20. New claim 32 replaces former claim 14. The claim has been amended to recite that the method claimed exhibits its effects in mammals. Support for the amendment can be found in, *inter alia*, the original claims. New claim 33 recites that the method of new claim 32 exhibits it effects in humans. Support for the amendment can be found in, *inter alia*, the original claims. New claim 34 recites that the antimetabolite compound of claim 32 or 33 is 5-fluorouricil or gemcitabine. Support for the claim can be found at, *inter alia*, page 2, lines 10-13. New claim 35 recites that the method of claim 32 or 33 is carried out by the simultaneous, separate or sequential administration of the alkylating anthracycline of formula Ia or Ib and the antimetabolite compound I. Support for the claim can be found at, *inter alia*, page 3, lines 5-20.

New claim 36 replaces former claim 16. The claim has been amended to recite that the method claimed exhibits its effects in mammals. Support for the amendment can be

found in, *inter alia*, the original claims. New claim 37 recites that the method of new claim 36 exhibits it effects in humans. Support for the amendment can be found in, *inter alia*, the original claims. New claim 38 recites that the antimetabolite compound of claim 36 or 37 is 5-fluorouricil or gemcitabine. Support for the claim can be found at, *inter alia*, page 2, lines 10-13. New claim 39 recites that the method of claim 36 or 37 is carried out by the simultaneous, separate or sequential administration of the alkylating anthracycline of formula Ia or Ib and the antimetabolite compound I. Support for the claim can be found at, *inter alia*, page 3, lines 5-20.

In addition, new claims 28, 32 and 36 have been amended to recite methods of treatment comprising administering the alkylating anthracycline of formula Ia or Ib and an antimetabolite compound as claimed in claim 1, as opposed to comprising administering the alkylating anthracycline of formula Ia or Ib as claimed in claim 1 and an antimetabolite compound, to improve clarity. Support for the amendments can be found at, *inter alia*, page 2, lines 19-32.

Former claim 15 has been canceled without prejudice or disclaimer and is not pursued in the new claim presented herein. Claims 17-39 are pending in this application.

All amendments are made without prejudice or disclaimer, and Applicants reserve the right to pursue the cancelled subject matter in a continuation application. No new matter is added by these amendments, and Applicants respectfully request their entry.

Rejection of Claims 15 Under 35 U.S.C. §112, First Paragraph

Claim 15 stands rejected for allegedly lacking enablement. However, claim 15 has been canceled thus rendering its rejection under § 112, first paragraph moot.

Rejection of Claims 3, 4 and 6 Under 35 U.S.C. §112, First Paragraph

Claims 3, 4 and 6 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. The Examiner asserts that the specification is enabling for gemcitabine but does not reasonably provide enablement for cytidine analogs, 5-fluoropyrimidine and 5-fluorouricil. Claims 3, 4, and 6 have been canceled and replaced

by new claims 21, 22, and 24, so the argument will proceed with the new claims in their stead. Applicants respectfully traverse the rejection and submit that the specification provides sufficient disclosure to enable one to make and use the claimed invention without undue experimentation.

The specification provides an example utilizing gemcitabine and formula Ia. Page 4, line 31 through page 5, line 33. However, the specification also provides enabling description for the use of antimetabolites beyond gemcitabine, such as cytidine analogs, 5-fluoropyrimidine and 5-fluorouricil. Specifically, the specification provides that "for the administration of the antimetabolite compound the course of therapy generally employed is from about 0.1 to about 10 g/m^2 of body surface area. More preferably, the course of therapy employed is from about 1 mg/m^2 to about 5 mg/m^2 of body surface area." Page 3, lines 27-32. In addition, the specification provides that "standard pharmaceutical preparations were used for antimetabolite compounds." Page 5, lines 26-28. "Standard pharmaceutical preparations" for the contemplated oral and parenteral administration (see, e.g., page 3, lines 5-8) are well known to one of skill in the art. *See, e.g., Remington's Pharmaceutical Sciences* (18th Ed., A.R. Gennaro, ed., Mack Publishing Company 1990. The specification provides disclosure that enables proper dosing of the antimetabolites of the invention, as well as proper formulations for the contemplated administration routes. Thus, Applicants submit that the specification is enabling for cyidine analogs, 5-fluoropyrimidine and 5-fluorouricil, in addition to gemcitabine, and, consequently, Applicants respectfully request that the § 112 first paragraph rejection of canceled claims 3, 4 and 6 (i.e., new claims 21, 22 and 24) be withdrawn.

Rejection of Claims 1-6 and 12-16 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6 and 12-16 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. Claims 1-6 have been canceled and replaced by new claims 17, 20-24. Claims 12, 13, 14 and 16 have been canceled and replaced by new claims 28, 30, 32 and 36,

respectively, with claim 15 not currently pursued in the new claims. The argument will proceed using the new claims in the canceled claims' stead. Applicants respectfully traverse.

The Examiner asserts that claim 1 (i.e., claim 17) is indefinite for reciting "simultaneous, separate or sequential" administration of the product of claim 1 as it is allegedly "not clear how the product containing the alkylating agent and the antimetabolite as a combined preparation can be used separately or sequentially."

The specification instructs one of skill in the art that the product of claim 1 represents a combination therapy and need not be part of a single formulation. For example, the specification recites:

> the term "administered" or "administering" as used herein is meant parenteral **and**/or oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration. . .the alkylating anthracycline may be administered simultaneously with the compound with the antimetabolite compound activity, for example 5-fluoropyrimidine or cytidine class, or the compounds may be administered sequentially, in either order. Page 3, lines 5-13; emphasis added.

In addition to the language cited above indicating that the alkylating anthracycline and the antimetabolite exist as separate entities in the treatment regimen, one of ordinary skill in the art would know that the use of different administration avenues, i.e., parenteral and oral, would require separate formulations due to the different requirements for active compound dissolution and release for each type of administration. *See, e.g., Remington's Pharmaceutical Sciences* (18th Ed., A.R. Gennaro, ed., Mack Publishing Company 1990. Further, the example, the description and results for which are in Table 1 at page 4, line 31 through page 5, line 24, demonstrates sequential administration of the combination therapy or combination preparation. Specifically, compound Ia was administered 2 hours after gemcitabine. Page 5, line 23-26; Table 1. Thus, it is clear from the specification that a combination preparation can be administered simultaneously, separately or sequentially.

Claims 2-6 (i.e., new claims 20-24) stand rejected as depending from an allegedly indefinite claim. In light of the above, Applicants respectfully request that these rejections be withdrawn.

Claims 12, 13, 14 and 16 (i.e., new claims 28, 30, 32 and 36) stand rejected as indefinite for allegedly failing to set forth the metes and bounds of the patent protection sought. Specifically, the Examiner bases the rejections on the use of a broad recitation of "mammal," followed by a specific recitation of "including a human" in the same claim. Claim 15 stands rejected on the same grounds but has been canceled, without replacement by a new claim, thus rendering its § 112, second paragraph rejection moot. Claims 12, 14 and 16 have been canceled and submitted as new claims 28, 32 and 36, respectively, to recite methods of treatment of mammals, with new claims 29, 33 and 37 reciting methods of treatment of humans. Claim 13 has been canceled and replaced by new claim 30. Thus amended, Applicants submit that the rejections are rendered moot.

Rejection of Claims 1-8 Under 35 U.S.C. §103

Claims 1-8 stand rejected under 35 U.S.C. § 103 as allegedly being obvious over Marchini et al. (Anti-Cancer Drug Design, 1995, 10, 641-653), in light of Suarato et al. (Anthracycline Antibiotics, 1995, 142-145), Elslager et al. (US 4,853,221), Viale et al. (Anti-Cancer Drugs, 1998, 9, 457-463), Koeffler et al. (Cancer, 1981, 48, 1958-1963), and Hertel et al., (Cancer Research, 1990, vol. 50, pp 4417-4422). The Examiner asserts that it would have been obvious for one of ordinary skill in the art at the time the invention was made to combine formula Ia or Ib with antimetabolites 5-fluorouricil and gemcitabine to make a product and composition for treatment of tumors. Claims 1-8 have been canceled and replaced by new claims 17, 20-25, and 27. The argument will proceed using the new claims in the canceled claims' stead. Applicants respectfully traverse.

Three basic criteria must be met to establish a case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or

to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP 2143.

With respect to claims 1-8 (i.e., new claims 17, 20-25, and 27), the present invention relates to products and pharmaceutical compositions that contain the alkylating anthracycline of either 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin ("formula Ia") or 4-demethoxy-N-,N-bis(2-chloroethyl)-4'-methanesulfonyl daunorubicin ("formula Ib"), and an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically. Therefore, to establish a case of obviousness, the combined references must provide (1) the motivation to combine formula Ia or formula Ib with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically; (2) a reasonable expectation of success of combining the above for a synergistic antineoplastic effect in mammals, or humans specifically; and (3) **all** of the claimed limitations in the combined prior art references. M.P.E.P. § 2143. The teaching or suggestion to combine formula Ia or formula Ib with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically, and the reasonable expectation of its success must **both** be found in the prior art, and must not be based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2143. Further, all of the claimed limitations must be taught or suggested in the combined prior art references. *In re Royka*, 490 F.2d

981, 180 U.S.P.Q. 580 (CCPA 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970).

In the present application, none of the references, alone or in combination, teach or suggest combining formula Ia or formula Ib with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a surprising and unexpectedly synergistic antineoplastic effect in mammals, or humans specifically.

Marchini

Marchini *et al.*, relates to the cytotoxic effects of formulas Ia and Ib on L1210 murine cell lines. Marchini *et al.*, does not teach or suggest combining formula Ia or formula Ib with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically. In fact, the Examiner concedes that Marchini does not teach "formulas Ia or Ib with an antimetabolite as a combined preparation in a synergistic amount for treatment of tumors." See page 8, Office Action of December 3, 2002. The combination of art cited in this rejection does not cure the deficiencies of Marchini.

Suarato

Suarato *et al.*, relates to tests of the cytotoxic effect of formula Ib on a leukemia cell line. The Examiner makes the same concession for Suarato *et al.*, as Marchini. Page 8, Office Action of December 3, 2002. As above, Suarato *et al.*, does not teach or suggest combining formula Ia or formula Ib with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically.

Elslager

Elslager *et al.*, relates to "administering an antineoplastic effective amount of 5-methyl-6-[[3,4,5-trimethoxyphenyl)amino]methyl]-2,4-quinazolinediamine [*trimetrexate*]

or a pharmaceutically acceptable salt thereof either alone or in combination with an antineoplastically effective amount of a compound *selected from the group consisting of*...5-fluoro-2,4(1H,3H)-pyrimidinedione [5-fluorouricil] or a pharmaceutically acceptable salt thereof..." Column 1, lines 57-68. Elslager *et al.*, demonstrates a synergistic effect with *trimetrexate* and compounds *selected from the group consisting of* 5-fluorouricil among others. As opposed to DNA intercalation and alkylation activity of formulas Ia and Ib (*both* of which are important in the antineoplastic activity of formulas Ia and Ib), trimetrexate is a DHFR inhibitor. Column 2, lines 10-15. Thus, trimetrexate is from a completely different class of antineoplastic compounds than formulas Ia or Ib. Elslager *et al.*, relates to trimetrexate and offers no teaching or suggestion that an alkylating anthracycline of formulas Ia or Ib could be combined with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically. Thus, Elslager *et al.*, fails to cure the deficiencies of the other cited references. Importantly, the disclosure of the combination of an antineoplastic compound with an antimetabolite does not automatically render obvious the combination of every other particular antineoplastic and antimetabolite, particularly when, for example, the antineoplastic compounds are distinct in composition, mode of action, results, etc.

Viale

Viale *et al.*, relates to administering cis-diamminechloro-[2-(diethylamino)ethyl 4-amino benzoate, N4]-chlorideplatinum(II) monohydrochloride monohydrate (or "DPR") with other drugs, including 5-fluorouricil. Page 457, abstract. Viale *et al.*, demonstrates a synergistic effect between DPR and 5-fluorouricil. As with Elslager *et al.*, platinum-based compounds are from a distinct set of anticancer compounds from those of formulas Ia and Ib. One of skill in the art would know that platinum-based antineoplastic drugs act by forming DNA adducts and thus operate through a different mechanism than formulas Ia and Ib. See, e.g., Drobnik J. Antitumor Activity of Platinum Complexes, Cancer

Chemotherapy Pharmacology, 1983; 10(3): 145-149. Thus, Viale *et al.*, also fails to cure the deficiencies of Marchini *et al.*, when combined with the other cited references.

Koeffler

Koeffler *et al.*, relates to the use of 5-azacytidine, alone, to treat acute myleogenous leukemia cells. See page 1958, abstract; 191, second full paragraph; Table 2. Koeffler *et al.*, offers no teaching or suggestion to combine 5-azacytidine with formula Ia or formula Ib. Koeffler *et al.*, also fails to teach or suggest the combination of an antimetabolite compound, a 5-fluoropyrimidine, or 5-fluorouricil specifically or an alternative cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically. Teaching the use of a cytidine analog that is contemplated by the present invention does not render the present invention obvious because Koeffler *et al.*, fails to teach or suggest combined use of the analog with formula Ia or Ib. Thus, Koeffler *et al.*, fails to cure the deficiencies of Marchini *et al.*, and the other cited references.

Hertel

Hertel *et al.*, relates to the use of gemcitabine, alone, as an antitumor drug. Hertel *et al.*, offers no guidance , let alone any specific teaching or suggestion, to combine gemcitabine (or other cytidine analog) with antineoplastic agents of formulas Ia or Ib to confer a synergistic antineoplastic effect in mammals, or humans specifically. Hertel *et al.*, also fails to teach or suggest the combination of formula Ia or formula Ib with a 5-fluoropyrimidine, or 5-fluorouricil specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically. As with Koeffler *et al.*, Hertel relates to the use of one of the components of the present invention, but it fails to teach or suggest all of the limitations of the present invention.

Applicants respectfully point out that "[t]he Federal Circuit has recently reemphasized the importance of the motivation to combine." *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*, 230 F.3d 1377 (Fed. Cir. 2000). "[B]road conclusory statements regarding the teaching of multiple references, standing

alone, are not evidence [of a motivation to combine]." *Ecolochem, Inc. v. southern California Edison Co.*, 227 F.3d 1361 (Fed. Cir. 2000). Accordingly, "the showing of combinability must be clear and particular." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654 (Fed. Cir. 2000). See also *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340 (Fed. Cir. 2000) ("[w]hen an obviousness determination is based on multiple prior art references, there must be a showing of some teaching, suggestion, or reason to combine the references....The showing of combinability, in whatever form, must nevertheless be clear and particular.")

Applicants submit that, in the absence of any further teaching, the disclosure of the use of certain compounds contemplated in the present invention, does not amount to a clear and particular motivation to combine the compounds of formulas Ia or Ib with an antimetabolite compound, a 5-fluoropyrimidine, or 5-fluorouricil specifically or an alternative cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically. The Examiner asserts that one of skill in the art would be motivated to combine the cited references since the references allegedly teach the desirability to use 5-fluorouricil in combination with other anticancer agents. Applicants respectfully submit that a reference that relates to gemcitabine and a reference that demonstrates synergistic effects with the combination of compounds completely unrelated to formula Ia or Ib cannot provide the motivation to combine formula Ia or Ib with the contemplated compound to confer a synergistic antineoplastic effect in mammals, or humans specifically. The Examiner's argument is one that would render all future non-obvious combinations allegedly obvious over a general reference relating to a compound utilized in an invention and a reference relating to a combination of compounds unrelated to those contemplated in the invention. Applicant's respectfully submit that such an argument does not defeat the present case because, in addition to failing to provide teaching or motivation to combine, the cited references fail to teach all of the claimed limitations as will be discussed below.

The Examiner also asserts that the synergistic effects and the ability to use less of a toxic anticancer agent co-administered with 5-fluorouricil and gemcitabine provides sufficient motivation to use combinations of these two antimetabolites with compounds of formulas Ia or Ib. A reference relating to synergistic effects between 5-fluorouricil or gemcitabine and compounds unrelated in structure or mechanism to formulas Ia and Ib does not render obvious their combination with formulas Ia and Ib. There is no teaching or suggestion in the cited references indicating the mechanism of synergy, or any teaching to suggest that such synergistic activity is likely to occur when combined with compounds unrelated to those with which they were combined in Elslager *et al.*, and Viale *et al.*, i.e., formulas Ia and Ib.

In addition to failing to provide the teaching or suggestion to combine the above compounds for a synergistic effect, no reference or combination of references provides a reasonable expectation of success of accomplishing the same activity, and **both** must be found in the prior art, and must not be based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2143. Applicants submit that such reasonable expectation of success is not found in the cited references.

Marchini *et al.*, and Suarato *et al.*, merely relate to the use of formulas Ia and Ib. Elslager *et al.*, Viale *et al.*, merely relates to the use of unrelated compounds with 5-fluorouricil. Koeffler *et al.*, and Hertel *et al.*, relate to the singular use of 5-azacytidine and gemcitabine, respectively. Though no references suggest that formulas Ia and Ib be utilized with the antimetabolites of the invention, the references that relate to the use of combinations of compounds, Elslager *et al.*, and Viale *et al.*, both indicate mixed results regarding synergism. Some compounds (sometimes) demonstrate synergism, for example doxorubicin (Viale, page 460; Elslager, column 8, Table 7, test 1) and cisplatin (Elslager, Table 7, test 1); whereas, some compounds (sometimes) do not, for example, taxol (Viale, page 462) and methotrexate (Viale, page 460). There is no obvious link between those combinations that work consistently and those that do not. Elslager *et al.*, and Viale *et al.*, both demonstrate that it is unknown what combinations will be synergistic, and,

therefore, the combination of the present invention is not obvious. Nothing ties the group of references together such that one would have a reasonable expectation of success of if one combined the compounds if formulas Ia or Ib with an antimetabolite compound, a 5-fluoropyrimidine, or 5-fluorouricil specifically or an alternative cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically. There is no reasonable expectation that a DNA intercalating, alkylating compound should demonstrate synergistic effects with, for example, 5-fluorouricil or gemcitabine beyond Applicants' specification.

The third requirement to establish an obviousness rejection is that all of the claimed limitations must be taught or suggested in the combined prior art references. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970). Contrary to the requirements put forth in *In re Wilson*, the cited references fail to provide all of the limitations of the instant claims as they fail to contemplate combining formula Ia or formula Ib with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a synergistic antineoplastic effect in mammals, or humans specifically.

Applicants respectfully submit that in determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). Applicants respectfully suggest that the combined teachings of the cited references do not render obvious the entire invention as claimed. Accordingly, withdrawal of the § 103 rejection against (canceled) claims 1-8 (i.e., new claims 17, 20-25 and 27) based on Marchini et al., in light of Suarato et al., Elslager et al., Viale et al., Koeffler et al., and Hertel et al., is in order and respectfully requested.

Rejection of Claims 12-16 Under 35 U.S.C. §103

Claims 12-16 also stand rejected under 35 U.S.C. § 103 as allegedly being obvious over Marchini et al., in light of Suarato et al., Elslager et al., Viale et al., Koeffler et al., and Hertel et al. Claims 12-16 have been canceled, and claims 12, 13, 14 and 16 have been replaced by new claims 28, 30, 32 and 36, respectively. Because claim 15 has been canceled without replacement in the new claims, the rejection is rendered moot. As above, the argument will proceed using the new claims in the canceled claims' stead. Applicants respectfully traverse.

With respect to claims 12-14 and 16 (i.e., new claims 28, 30, 32 and 36), the present invention relates to methods of treating tumors and metastasis in a mammal and a method of treating a tumor by the inhibition of angiogenesis in a mammal, in all cases utilizing the product of claim 1 (i.e., new claim 17). In the present application, none of the references, alone or in combination, teach or suggest methods of treatment in which formula Ia or formula Ib are combined with an antimetabolite compound generally, a 5-fluoropyrimidine, or 5-fluorouricil specifically, or a cytidine analog, or gemcitabine specifically, to confer a surprising and unexpectedly synergistic antineoplastic effect in mammals, or humans specifically. Applicants submit that as the cited references do not render obvious the products and pharmaceutical composition of the invention, neither do they render obvious methods that require their utilization. Specifically, the cited references fail to teach or suggest, offer a reasonable expectation of success of or specify all of the claimed limitations related to the instant methods.

Conclusion

In light of the above, Applicants respectfully submit that the claims are in order and request that the Examiner pass the application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below..

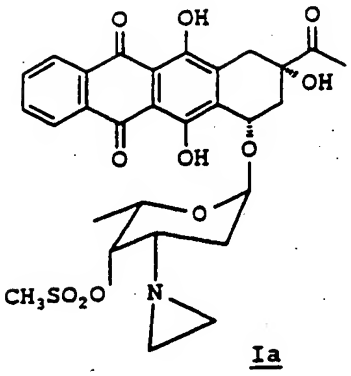
Respectfully submitted,

Date: 4/3/03 by: _____

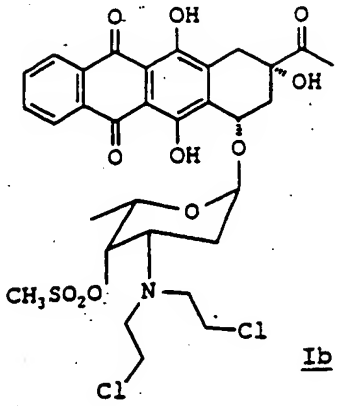
Emily Miao
Reg. No. 35,285

Appendix A
Clean Version of the Amendments

17. (New) A product containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and an antimetabolite compound as a combined preparation that has a synergistic antineoplastic effect for simultaneous, separate or sequential use in treatment of tumors in mammals.

18. (New) The product according to claim 17, further containing a pharmaceutically acceptable carrier or excipient.

19. (New) The product according to claim 17 or claim 18, wherein the mammal is a human.

20. (New) The product according to claim 17 or claim 18 wherein the alkylating anthracycline is a 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methanesulfonyl daunorubicin.

21. (New) A product according to claim 17 or claim 18 wherein the antimetabolite compound is a cytidine analog.

22. (New) A product according to claim 17 or claim 18 wherein the antimetabolite compound is a 5-fluoropyrimidine.

23. (New) A product according to claim 21 wherein the cytidine analog is gemcitabine.

24. (New) A product according to claim 22 wherein the 5-fluoropyrimidine is 5-fluorouricil.

25. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as an active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 17 and an antimetabolite compound that has a synergistic antineoplastic effect in mammals when administered simultaneously, separately or sequentially.

26. (New) A pharmaceutical composition according to claim 25 wherein the mammal is a human.

27 (New) A pharmaceutical composition according to claim 25 or claim 26 wherein the antimetabolite compound is 5-fluorouricil or gemcitabine.

28. (New) A method for treating tumors in a mammal in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib and an antimetabolite compound as claimed in claim 17 or claim 18 to said mammal in a synergistic antineoplastic effective amount.

29. (New) The method according to claim 28 wherein the mammal is a human.

30. (New) The method according to claim 28 or claim 29 wherein the antimetabolite compound is 5-fluorouricil or gemcitabine.

31. (New) The method according to claim 28 or claim 29 wherein a synergistic antineoplastic effective amount of the alkylating anthracycline of formula Ia or Ib and the antimetabolite compound I are administered simultaneously, separately or sequentially.

32. (New) A method for treatment of metastasis in a mammal in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib and an antimetabolite compound as claimed in claim 17 or claim 18 to said mammal in a synergistic antineoplastic effective amount.

33. (New) The method according to claim 32 wherein the mammal is a human.

34. (New) The method according to claim 32 or claim 33 wherein the antimetabolite compound is 5-fluorouricil or gemcitabine.

35. (New) The method according to claim 32 or claim 33 wherein a synergistic antineoplastic effective amount of the alkylating anthracycline of formula Ia or Ib and the antimetabolite compound I are administered simultaneously, separately or sequentially.

36. (New) A method for treating a tumor by the inhibition of angiogenesis in a mammal in need thereof, comprising administering the alkylating anthracycline of formula Ia or Ib and an antimetabolite compound as claimed in claim 17 or claim 18 to said mammal in a synergistic antineoplastic effective amount.

37. (New) The method according to claim 36 wherein the mammal is a human.

38. (New) The method according to claim 36 or claim 37 wherein the antimetabolite compound is 5-fluorouricil or gemcitabine.

39. (New) The method according to claim 36 or claim 37 wherein a synergistic antineoplastic effective amount of the alkylating anthracycline of formula Ia or Ib and the antimetabolite compound I are administered simultaneously, separately or sequentially.